Evaluation of autonomic dysfunction in patients with hepatic cirrhosis

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CERTIFICATE

This is to certify that the dissertation titled "**Evaluation of Autonomic Dysfunction in Patients with Hepatic Cirrhosis**" is a genuine work done by Dr.E.Kandasamy alias Kumar, Post Graduate in Medical Gastroenterology under my supervision between April 2006 to March 2007 and is being submitted for the partial fulfillment of the requirement for the awarding of D.M. (Medical Gastroenterology) degree by the Tamilnadu Dr. M.G.R Medical University, Chennai.

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CONTENTS

Evaluation of Autonomic Dysfunction in Patients with Hepatic Cirrhosis

1. Introduction:

Cirrhosis of the liver leads to a number of complications, some of which may eventually prove fatal. For more than a century, chronic alcoholics have been known to have peripheral neuropathy. It has been observed that alcoholics with liver damage have higher frequency of neuropathy than those without it. There are reports of association of chronic liver disease with autonomic neuropathy However; conflicting reports have also appeared causing much confusion. Patients with cirrhosis and portal hypertension develop hyper dynamic circulation, with increased blood volume and cardiac output, and with a reduced peripheral vascular resistance. This disorder has been related to portal hypertension–induced arterial vasodilatation in the peripheral and splanchnic beds, but other factors may contribute, such as abnormally high levels of circulating vasodilators and false neurotransmitters.[1]

Alterations in the autonomic nervous system's drive to the heart and circulation may also occur in cirrhosis, as suggested by studies based on cardiovascular tests such as cardiovascular responsiveness to postural changes, exercise, and mental stress. These tests, however, have been criticized for being insensitive to early changes in the autonomic function, especially in the sympathetic nervous system. Recent evidence indicates that the spontaneous, small beat-to-beat fluctuations that are usually observed in

the continuous recordings of heart rate and arterial pressure reflect the activity of the efferent arc of the autonomic nervous sys tem that is modulating cardiovascular function. In particular, sympathetic and vagal outflows to the heart and circulation generate two main oscillatory rhythms: (1) a short-term rhythm, present in heart period and arterial pressure variabilities and defined as the low-frequency (LF) component, which is considered a marker of the sympathetic activity; and (2) a long-term rhythm, only occurring in heart period variability, related to respiration, and known as the high frequency (HF) component, which is thought to be a marker of the vagal modulation. These oscillatory components of heart rate and arterial pressure signals can be extracted from the variability signals through spectral analysis techniques.

2. Back ground :

Neural regulation of the gastrointestinal tract

The enteric nervous system plays an integral role in the regulation of gut mucosal and motor function. It is organized into two major plexuses. The myenteric plexus lies between the external longitudinal and internal circular muscle layers. The submucosal plexus lies between the circular muscle layer and the mucosa.[2] Although the enteric nervous system receives input from the central and autonomic nervous systems, it can function independently. Nerves of the myenteric plexus project fibers primarily to the smooth muscle of the gut, with only a few axons extending to the submucosal plexus. Most of the fibers of the submucosal plexus project into the mucosa and the submucosal and myenteric plexuses.

Figure :1 Pathways of sympathetic and parasympathetic innervations

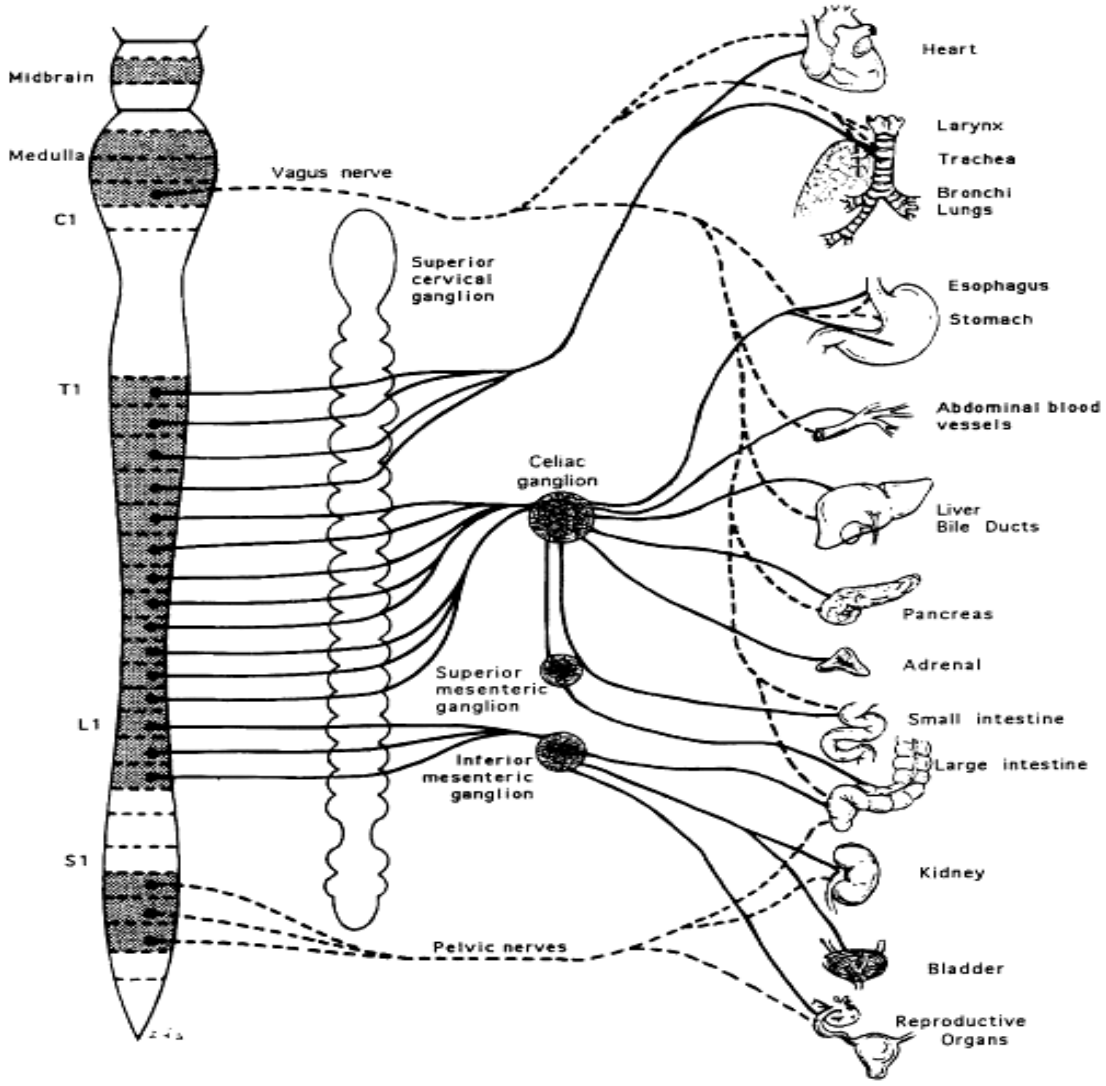
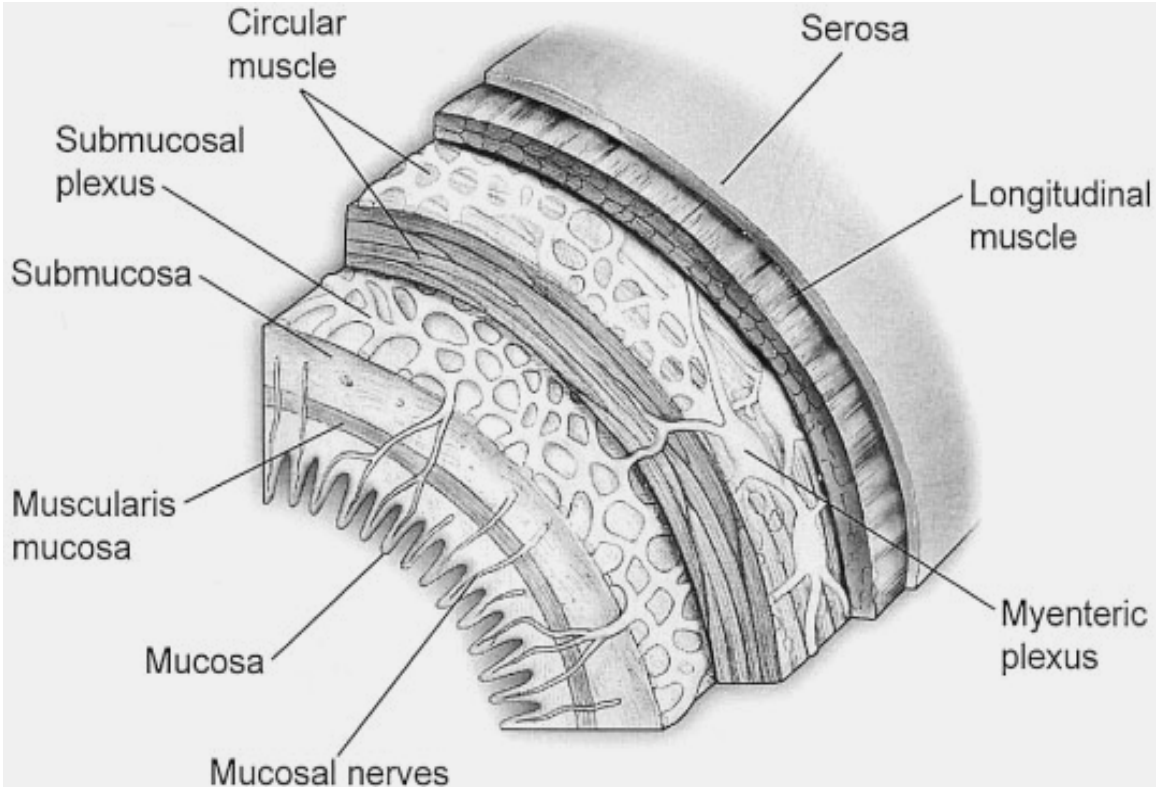


Figure 2. Organization of the enteric nervous system



Various peptide and nonpeptide neurotransmitters are found in the enteric nervous system[3]. Recent studies using immunohistochemical staining have localized neurotransmitters to specific neurons in the gastrointestinal tract. γ -Aminobutyric acid is found primarily in the myenteric plexus and is involved in regulating smooth muscle contraction. Serotonin is found within the plexus and functions as an interneuron transmitter. Adrenergic neurons originate in ganglia of the autonomic nervous system and synapse with enteric neurons. Peptides such as neuropeptide Y (NPY) are often secreted from the same adrenergic neurons and generally exert inhibitory effects such as vasoconstriction.[4] Other adrenergic neurons containing somatostatin project to the submucosal plexus, where they inhibit intestinal secretion. Coexistence of peptides and neurotransmitters in the same neurons is not unusual; in fact, the interplay among transmitters is critical for coordinated neural regulation.[5] For example, the peptides VIP and peptide histidine isoleucine (PHI) are commonly found together, as are the tachykinins substance P and substance K, where they have complementary effects. Somatostatin is found in interneurons that project caudally. The inhibitory action of somatostatin is consistent with a role in causing muscle relaxation in advance of a peristaltic wave. The abundance of VIP in the myenteric plexus also suggests that its inhibitory actions are important for smooth muscle relaxation in gut motility. VIP neurons that project from the submucosal plexus to the mucosa most likely stimulate intestinal fluid secretion. Other neurons that innervate the mucosa contain acetylcholine.Mucosal cells of the intestine contain receptors for both VIP and acetylcholine, allowing these transmitters to exert synergistic effects, because VIP

increases intracellular cyclic adenosine monophosphate (cAMP) levels and acetylcholine increases intracellular calcium in the target cell.[6]

Bipolar neurons that project to the mucosa and myenteric plexus act as sensory neurons and often contain substance P and acetylcholine as neurotransmitters. These neurons participate in pain pathways and modulate inflammation.The ability of hormones to act on nerves locally within the submucosa of the intestine and affect more distant sites on nerves such as the vagus expands the potential organs that may be regulated by gut hormones. Chemical and mechanical stimuli cause the release of hormones from endocrine cells of the intestinal mucosa. These interactions initiate a wide variety of secretomotor responses, many of which are mediated by enteric neurons. Secretomotor circuits consist of intrinsic primary afferent neurons with nerve endings in the mucosa and extension through the myenteric and submucosal plexuses. This circuitry allows nerves to stimulate mucosal cells to secrete fluid and electrolytes and at the same time stimulate muscle contraction. The same motor neurons also have axons that supply arterioles and can initiate vasodilator reflexes. Extrinsic primary afferent neurons can be either of the vagus, with somal bodies in the nodose ganglia and axons that reach the gut through the vagus nerve, or of the spinal nerves of the thoracic and lumbar regions, whose cell bodies lie in the dorsal root ganglia. Information conducted by extrinsic primary afferent neurons includes pain, heat, and sensations of fullness or emptiness. These neurons are also targets for hormones. For example, the satiety effect of CCK in the bloodstream is mediated through the vagus nerve. Specific CCK receptors have been identified on the vagus, and blockade of these receptors abolishes the satiation induced by peripheral CCK.[7]

Endocrine, paracrine, and neural transmitters existing within the lamina propria modulate effects on the gut immune system. Lymphocytes, macrophages, mast cells, neutrophils, and eosinophils are potential targets for endocrine and neural transmitters and participate in the inflammatory cascade. Moreover, inflammatory mediators can act directly on enteric nerves. Serotonin released from endocrine cells is involved in intestinal anaphylaxis and stimulates vagal afferent fibers that possess the 5-hydroxytryptamine 3 5-HT_3) receptor.

Chemical messengers of the gastrointestinal tract

The enteric nervous system, through intrinsic and extrinsic neural circuits, controls gastrointestinal function. This control is mediated by a variety of chemical messengers, including motor and sensory pathways of the sympathetic and parasympathetic nervous systems. The parasympathetic preganglionic input is provided by cholinergic neurons and elicits excitatory effects on gastrointestinal motility via nicotinic and muscarinic receptors, whereas the sympathetic input occurs by postganglionic adrenergic neurons.

Acetylcholine

Acetylcholine is synthesized in cholinergic neurons and is the principal regulator of gastrointestinal motility as well as pancreatic secretion. Acetylcholine is stored in nerve terminals and released by nerve depolarization. Released acetylcholine is then able to bind to postsynaptic muscarinic and/or nicotinic receptors. Nicotinic acetylcholine receptors belong to a family of ligand-gated ion channels and are homopentamers or heteropentamers comprised of α, β , γ , δ , and ε subunits The α subunit is believed to be

the mediator of postsynaptic membrane depolarization following acetylcholine receptor binding. Muscarinic receptors belong to the heptahelical GPCR family. There are five known muscarinic cholinergic receptors (M_1 to M_5). Muscarinic receptors can be further classified based on receptor signal transduction, with M_1, M_3, and M_5 stimulating adenylate cyclase and M_2 and M_4 inhibiting this enzyme.

Acetylcholine is degraded by the enzyme acetylcholinesterase, and the products may be recycled through high-affinity transporters on the nerve terminal

Catecholamines

The primary catecholamine neurotransmitters of the enteric nervous system include norepinephrine and dopamine. Norepinephrine is synthesized from tyrosine and released from postganglionic sympathetic nerve terminals that innervate enteric ganglia and blood vessels. Tyrosine is converted to dopa by tyrosine hydroxylase. Dopa is initially converted into dopamine by dopa decarboxylase and packaged into secretory granules. Norepinephrine is formed from dopamine by the action of dopamine β -hydroxylase within the secretory granule. After an appropriate stimulus, norepinephrine-containing secretory granules are released from nerve terminals and bind to adrenergic receptors.

Adrenergic receptors are G protein coupled, have seven typical membrane-spanning domains, and are of two basic types: α and β . α-Adrenergic receptors are further classified into $\alpha1_A$, $\alpha1_B$, $\alpha2_A$, $\alpha2_B$, $\alpha2_C$, and $\alpha2_D$. Similarly, β receptors include β_1, β_2, and β_3. Adrenergic receptors are known to signal through a variety of G proteins, resulting in stimulation or inhibition of adenylate cyclase and other effector systems.

Norepinephrine signaling is terminated by intracellular monoamine oxidase or by rapid reuptake by an amine transporter. The actions of adrenergic receptor stimulation regulate smooth muscle contraction, intestinal blood flow, and gastrointestinal secretion.[8]

Dopamine is an important mediator of gastrointestinal secretion, absorption, and motility and is the predominant catecholamine neurotransmitter of the central and peripheral nervous systems. In the central nervous system, dopamine regulates food intake, emotions, and endocrine responses, and peripherally, it controls hormone secretion, vascular tone, and gastrointestinal motility.[9] Characterization of dopamine in the gastrointestinal tract has been challenging for several reasons. First, dopamine can produce inhibitory and excitatory effects on gastrointestinal motility. Generally, the excitatory response, which is mediated by presynaptic receptors, occurs at a lower agonist concentration than the inhibitory effect that is mediated by postsynaptic receptors. Second, localization of dopamine receptors has been hampered by identification of dopamine receptors in locations that appear to be species specific. Finally, studies of dopamine in gastrointestinal tract motility have often used pharmacologic amounts of this agonist. Therefore, interpretation of results has been confounded by the ability of dopamine to activate adrenergic receptors at high doses.

Classically, dopamine was thought to act via two distinct receptor subtypes: type 1 and type 2. Molecular cloning has now demonstrated five dopamine receptor subtypes, each with a unique molecular structure and gene locus. Dopamine receptors are integral membrane GPCRs, and each receptor subtype has a specific pharmacologic profile when

exposed to agonists and antagonists. After release from the nerve terminal, dopamine is cleared from the synaptic cleft by a specific dopamine transporter.

Serotonin

Serotonin has long been known to play a role in gastrointestinal neurotransmission. The gastrointestinal tract contains more than 95% of the total body serotonin, and serotonin is important in a variety of processes, including nausea, emesis, epithelial secretion, and bowel motility. Serotonin is synthesized from tryptophan, an essential AA, and is converted to its active form in nerve terminals. Serotonin is inactivated in the synaptic cleft by reuptake via a serotonin-specific transporter. Most plasma serotonin is derived from the gut, where it is found in mucosal enterochromaffin cells and the enteric nervous system. Serotonin mediates its effects by binding to a specific receptor. There are seven different serotonin receptor subtypes found on enteric neurons, enterochromaffin cells, and gastrointestinal smooth muscle (5-HT_1 to 5-HT_7). Through these receptors serotonin regulates intestinal secretion, absorption, and motility.

Serotonin, and its receptor, has been implicated in the pathogenesis of irritable bowel syndrome, as well as constipation and diarrhea. The myenteric plexus contains serotonic interneurons that project to the submucosal plexus as well as ganglia extrinsic to the bowel wall. Extrinsic neurons activated by serotonin participate in bowel sensation and may be responsible for abdominal pain, nausea, and symptoms associated with irritable bowel syndrome. Intrinsic neurons activated by serotonin are primary components of the peristaltic and secretory reflexes responsible for normal gastrointestinal function.

Characterization of specific serotonin receptor subtypes has led to the development of selective agonists and antagonists for the treatment of gastrointestinal disorders such as irritable bowel syndrome and chronic constipation and diarrhea. For example, 5-HT_3 receptor antagonists may be useful in diarrhea-predominant irritable bowel syndrome, and the 5-HT_4 receptor agonist has prokinetic effects and may be useful in constipation or other motility disorders.

Histamine

In the gastrointestinal tract, histamine is best known for its central role in regulating gastric acid secretion and intestinal motility. Histamine is produced by enterochromaffin-like cells of the stomach and intestine as well as enteric nerves. Histamine is synthesized from *l*-histidine by histidine decarboxylase and activates three GPCR subtypes. H_1 receptors are found on smooth muscle and vascular endothelial cells and result in activation of phospholipase C (PLC). As such, the H_1 receptor mediates many of the allergic responses induced by histamine. H_2 receptors are present on gastric parietal cells, smooth muscle, and cardiac myocytes. H_2 receptor binding stimulates Gs and activates adenylate cyclase. H_3 receptors are present in the central nervous system and gastrointestinal tract endochromaffin cells. These receptors signal through Gi and inhibit adenylate cyclase. Histamine can also interact with the*N*-methyl-*d*-aspartate (NMDA) receptor and enhance activity of NMDA-bearing neurons independent of the three known histamine receptor subtypes.

Unlike other neurotransmitters, there is no known trans porter responsible for termination of histamine's action. However, histamine is metabolized to telemethylhistamine by histamine *N*-methyltransferase, and is then degraded to telemethylimidazoleacetic acid by monoamine oxidase B and an aldehyde dehydrogenase.

Nitric Oxide

Although smooth muscle physiologists have long known of an "endothelial-derived relaxing factor" responsible for vasodilation, it took many years for the chemical nature of this substance to be identified as nitric oxide (NO). NO is a unique chemical messenger produced with citrulline from *l*-arginine and oxygen by the enzyme nitric oxide synthase (NOS). Three types of NOS are known. Types I and III are also know as *endothelial NOS* and *neuronal NOS* and are constitutively active. Small changes in NOS activity can occur through elevations in intracellular calcium. The inducible form of NOS (type II) is apparent only when cells become activated by specific cytokines and inflammation. This form of NOS is capable of producing large amounts of NO and is calcium independent. NOS is often colocalized with VIP and PACAP in neurons of the enteric nervous system. [10]

NO, being an unstable gas, has a relatively short half-life. Unlike most neurotransmitters and hormones, NO does not act via a membrane-bound receptor. Instead, NO readily diffuses into adjacent cells to directly activate guanylate cyclase. NO activity is terminated by oxidation to nitrate and nitrite. The role of NO in gastrointestinal

physiology includes stimulation of epithelial secretion, vasodilation, and mucosal defense.

Adenosine

Adenosine is an endogenous nucleoside that acts through any of four GPCR subtypes. Adenosine causes relaxation of intestinal smooth muscle and stimulates intestinal secretion. Adenosine can also cause peripheral vasodilation and activation of nociceptors that participate in pain neural pathways.

Cytokines

Cytokines are a group of polypeptides produced by a variety of immunomodulatory cells and are involved in cell proliferation, immunity, and inflammation. Cytokines are induced by specific stimuli, such as toxins produced by pathogens, and often elicit a complex variety of other cellular mediators to eradicate the foreign substance. Cytokines may be categorized as interleukins (ILs), tumor necrosis factors (TNFs), lymphotoxins, interferons, colony-stimulating factors (CSFs), and others. Interleukins can be further subtyped into 17 separate substances: IL-1 to IL-17. There are two TNFs: TNF-α and TNF-β , which are also known as lymphotoxin-α. Interferons are produced during viral or bacterial infection and come in two varieties: interferon-α (also known as leukocyte-derived interferon or interferon-β) and interferon-γ . Interferon-α is produced by T lymphocytes and is used clinically in the treatment of viral hepatitis. The major CSFs are granulocyte/mononuclear phagocyte-CSF, mononuclear phagocyte-CSF, and granulocyte-CSF. These agents are used in chemotherapy-induced neutropenia and

marrow support after bone marrow transplantation. Chemokines initiate and propagate inflammation and are of two groups: CXC (α chemokines) and CC (β chemokines). Other cytokines, such as transforming growth factor (TGF)-β and platelet-derived growth factor (PDGF), have proliferative effects.

Normal Liver Blood Flow

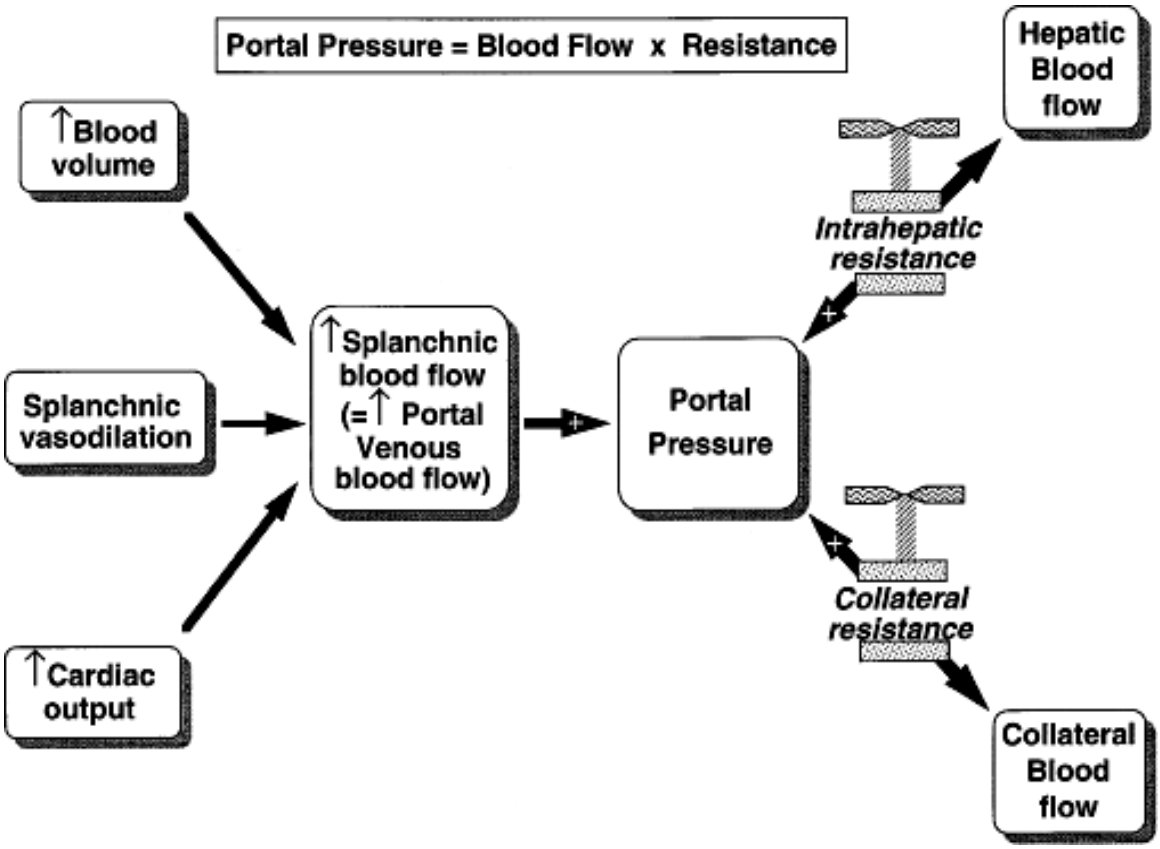
Hepatic blood flow is normally about 1500 mL/minute, representing 15% to 20% of cardiac output. One third of this flow and 30% to 60% of the oxygen consumed by the liver are provided by the hepatic artery. Approximately two thirds of the hepatic blood supply is provided by portal venous blood.[7,11] The high-pressure, well-oxygenated arterial blood mixes completely with the low-pressure, low-oxygen-containing, nutrient-rich portal venous blood within the hepatic sinusoids. After perfusing the sinusoids, blood flows, sequentially, into the hepatic venules, hepatic veins, and inferior vena cava. A fraction of the plasma entering the space of Disse is drained into lymphatic vessels.

A unique feature of the normal hepatic sinusoidal microcirculation is its low perfusion pressure. This low pressure is attributed to the unusually high precapillary to postcapillary resistance in the liver.[11] It appears that the sinusoids are normally protected from upstream portal perfusion pressure and fluctuations in that pressure by a presinusoidal site of high resistance, probably within the terminal portal venous radicals. Because the sinusoids are lined by an endothelium that lacks a continuous basement membrane and contains a multitude of large (50 to 200 nm), highly permeable fenestrae,

maintenance of a low pressure in the hepatic sinusoids is critical to the maintenance of normal rates of transudation of sinusoidal fluid into the space of Disse.

Another feature that is unique to the hepatic circulation is the close interrelationship between blood flow in the portal vein and that in the hepatic artery. When portal blood flow increases, hepatic arterial flow decreases; when portal flow decreases, hepatic arterial flow increases. This phenomenon has been termed the *hepatic arterial buffer response* and is an adenosine-mediated vascular reflex that ensures the maintenance of a relatively constant state of sinusoidal perfusion in the face of changes in portal inflow that occur, for example, with meals.

Figure 3. Hemodynamic principles in portal hypertension



Hyperdynamic circulation is a common and long-recognized feature of patients with advanced cirrhosis, consisting of elevated cardiac rate and output and reduced peripheral vascular resistance, so that arterial pressure is tendentially or frankly reduced. The clinical importance of this disorder was shown by subsequent studies, showing that the alterations of systemic hemodynamics, renal function, and vasoactive systems are prognostic indicators even more accurate than the tests exploring liver function. The setting of the hyperdynamic circulatory syndrome is the pathogenetic background of complications such as renal sodium and water retention and hepatorenal syndrome.Splanchnic blood pooling, opening of portal-systemic collaterals, and arterial vasodilatation, as well as a compensatory increase in blood volume, are the causative events of the hyperdynamic circulatory syndrome. The pathogenesis of arterial vasodilatation is still debated. It has been proposed that an overproduction of a variety of vasorelaxant agents, such as histamine, adenosine, gut-derived peptides and endothelial cell-derived vasodilators, and bile acid retention reduce the responsiveness of the vascular bed to endogenous vasoconstrictor stimuli.

There is abundant evidence for increased sympathetic nervous system tone in patients with cirrhosis. Serum norepinephrine levels are increased. However, considerable data point to the attenuation of sympathetic neurotransmitter effects in portal hypertension, in part as a result of down-regulation of adrenergic receptor density and in part as a result of postreceptor antagonism by opposing vasodilator influences.

Earlier studies showed that cross-perfusion between portal hypertensive and normal animals produces arteriolar vasodilation in the latter, lending support to the hypothesis that a transferable humoral vasodilator is present in the blood in portal hypertension. Much attention has since focused on putative vasoactive mediators responsible for the arteriolar vasodilation in splanchnic organs that underlies the increase in portal venous inflow. Investigators have postulated that endogenous vasodilators normally present in portal blood and cleared by the liver may escape hepatic removal either as a result of portosystemic shunting via portosystemic collaterals or as a result of impaired hepatocellular metabolism. A further possibility is that liver disease and portal hypertension lead to an increase in the production of certain vasodilators within either the hepatic or the splanchnic vascular beds. These vasodilators then reach high concentrations in the systemic circulation, thereby leading to systemic and splanchnic arterial vasodilation.

Several gut peptide hormones have been proposed as vasodilator mediators in portal hypertension. Glucagon has been a prime candidate. Serum glucagon levels are increased in experimental models of portal hypertension and in patients with cirrhosis.Glucagon impairs systemic vascular sensitivity to norepinephrine A role for glucagon in portal hypertension is also supported by the finding of a significant reduction in splanchnic blood flow after infusion of a glucagon-specific antiserum However, this reduction in splanchnic blood flow was not accompanied by a reduction in systemic vasodilation. In addition, other investigators have found no correlation between the magnitude of arterial vasodilation and circulating levels of glucagon On the other hand, infusion of

pharmacologic doses of somatostatin or its synthetic analog octreotide, which decreases glucagon release, produces vasoconstriction of both the splanchnic and the systemic circulation. Because somatostatin also inhibits the release of several other peptide vasodilators, such as substance P, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP), it is conceivable that the effects of somatostatin on the circulation in portal hypertension may be mediated by other peptides in addition to, or apart from, glucagon. Also, somatostatin may exert a direct vasoconstrictive effect on vascular smooth muscle. Therefore, understanding of the role of glucagon as a mediator of systemic vasodilation in portal hypertension remains inconclusive, but on the basis of available data, hyperglucagonemia may account for approximately 30% to 40% of the splanchnic vasodilation of chronic portal hypertension.

Vasoactive factors produced by the vascular endothelium have attracted considerable attention with respect to a potential role in the pathogenesis of portal hypertension. There is increasing evidence for the involvement of nitric oxide (NO) and prostacyclin in the pathogenesis of the circulatory abnormalities in portal hypertension.

NO is a powerful endogenous vasodilator that is generated in several tissues by a constitutive vascular endothelial NO synthase (eNOS) and an inducible NO synthase (iNOS) from the amino acid *l*-arginine. NO is produced constitutively by eNOS and by liver parenchymal and nonparenchymal cells after induction of iNOS by cytokines and endotoxin. An increasing body of evidence suggests that excessive NO biosynthesis by eNOS may be involved in the pathogenesis of the low systemic and splanchnic vascular

resistance and hence increased splanchnic arterial flow associated with portal hypertension.

Tumor necrosis factor-α (TNF-α) mediates the effects of endotoxin, a potent stimulant of NOS. A dramatic amelioration in the hyperdynamic circulation and the increased portal pressure has been described in portal hypertensive rats treated with antibody to TNF-α.

Administration of specific NO antagonists to animals with portal hypertension induces splanchnic and systemic vasoconstriction, thereby attenuating the hyperdynamic circulation. In addition, inhibition of NO synthesis, at least partially, corrects the blunted vascular responsiveness to vasoconstrictors that is characteristic of portal hypertension. The finding that patients with cirrhosis have increased serum and urinary concentrations of nitrite and nitrate (end-products of NO oxidation) also supports a role for NO in the genesis of the circulatory disturbances of portal hypertension. However, NO inhibition attenuates but does not normalize the hyperkinetic state of portal hypertension. Also, in one study chronic NO inhibition delayed but did not prevent the development of splanchnic vasodilation in experimental animals. These and other data suggest that other factors in addition to NO are involved in the vasodilatory phenomena associated with the hyperdynamic circulation of portal hypertension.

Several studies have supported a role for prostaglandins in the hyperdynamic circulation of portal hypertension. Prostacyclin levels have also been found to be increased in the portal vein of portal hypertensive rats, whereas patients with cirrhosis have increased systemic and portal levels of prostacyclin. Portal levels of prostacyclin correlate with the

degree of portal pressure elevation in these patients. In one study inhibition of prostaglandin biosynthesis by indomethacin reduced the hyperdynamic circulation and portal pressure in patients who had cirrhosis and portal hypertension.

A variety of other circulating vasodilators have been evaluated, including bile acids, histamine, adenosine, and substance P without convincing evidence to date that they contribute to the systemic hyperdynamic state of portal hypertension.

The autonomic nervous system plays a central role in modulating cardiac performance and vasomotor activity. The presence of an autonomic dysfunction (AD) in cirrhosis has been clearly shown through different experimental approaches, including the evaluation of the cardiovascular and sudomotor responses to physiological and pharmacological stimulation, and by showing a hyperproduction of weak adrenergic neurotransmitters. It has also been reported that the severity of AD is proportional to the severity of cirrhosis, and its presence is an indicator of poor prognosis in patients with both early and advanced liver disease.[12] Finally, AD is associated with an impairment of free water generation and hyponatremia and is likely involved in the pathogenesis of prolonged electrocardiographic Q-T interval, a common finding in advanced cirrhosis with an adverse prognostic significance. Based on the previous discussion, we hypothesized that AD is involved in the pathophysiology of hyperdynamic circulation of advanced cirrhosis.

The hyperdynamic circulation begins in the portal venous bed as a consequence of portal hypertension due to the increased resistance to flow from altered hepatic vascular morphology of chronic liver disease. Dilatation of the portal vein is associated with increased blood flow, as well as the opening up or formation of veno-venous shunts and splenomegaly. At the same time, portal hypertension leads to subclinical sodium retention resulting in expansion of all body fluid compartments, including the systemic and central blood volumes.

As liver disease progresses and liver function deteriorates, the systemic hyperdynamic circulation becomes more manifest with activation of the renin angiotensin--aldosterone system. The presence of vasodilatation in the presence of highly elevated levels of circulating vasoconstrictors may be explained by vascular hyporesponsiveness due to increased levels of vasodilators such as nitric oxide, as well as the development of an autonomic neuropathy. However, vasodilatation is not generalized, but confined to certain vascular beds, such as the splanchnic and pulmonary beds. Even here, the status may change with the natural history of the disease, since even portal blood flow may decrease and become reversed with advanced disease. The failure of these changes to reverse following liver transplantation may be due to remodeling and angiogenesis. Autonomic dysfunction (AD) is seen in both alcohol-induced and non-alcohol- induced liver disease, and when present is an independent predictor of mortality.[13] It is postulated that patients who were awaiting liver transplantation are likely to have a high prevalence of autonomic dysfunction with an associated increase in mortality Kaplan-Meier survival analysis showed a significantly higher mortality (P=.05) in patients with AN. On the basis of this observation, consideration should be given for

early liver transplantation in patients with advanced liver disease and autonomic dysfunction

Alcohol related neuropathy

The clinical symptoms of alcoholic peripheral neuropathy were described more than 200 years ago. The descriptions by Lettsom (1787) and Jackson (1822) have led to the recognition and association of peripheral nerve disease with excessive ethanol use. Several terms connote alcohol neuropathy, including neuritic beriberi, neuropathic beriberi, and alcoholic neuritis. In patients with alcoholic neuropathy, nutritional deficiency goes hand in hand with alcohol abuse.

The similarity between beriberi and alcoholic neuropathy had long been noted, but Shattuck in 1928 was the first to seriously discuss the relationship. He suggested that "polyneuritis of chronic alcoholism" was caused chiefly by failure to take or assimilate food containing a sufficient quantity of vitamin Bcomlex and might properly be regarded as true beriberi. However, this theory may be only partly true.

Pathophysiology: The precise pathogenesis of alcohol neuropathy and autonomic dysfunction remains unclear. Separating ethanol use from nutritional and vitamin deficiencies, especially thiamine, has always been difficult and a source of long-standing debate. Nutritional deficiency (frequently associated with alcohol neuropathy) and/or the direct toxic effect of alcohol or both have been implicated and studied. In Wernicke-Korsakoff syndrome, a clear association between reduction of thiamine levels or

thiamine-mediated enzyme activity (transketolase) has been established, though this has not been conclusively established in the case of peripheral neuropathy.

In their comparison of alcoholics and nonalcoholic control subjects, Behse and Buchthal concluded that nutritional deficiencies alone did not produce the neuropathy. Monforte et al concluded that alcohol appears to be toxic to autonomic and peripheral nerves in a dose-dependent manner, on the basis of heart rate, blood pressure, and electrophysiologic examination. In a study of macaque monkeys, Hallet et al failed to produce clinical and electrophysiologic signs of neuropathy in monkeys that were given a certain amount of alcohol for 3-5 years.

Studies in rats also failed to demonstrate a direct toxic effect of alcohol on the peripheral nerves. Most studies of peripheral neuropathy in humans and animals implicate nutritional deficiency as an etiology as opposed to the direct toxic effect of alcohol.[13,14]

Frequency:

Internationally: Depending on criteria and patient selection, incidence of peripheral neuropathy ranging from 10-50% has been reported. These studies included alcoholics hospitalized for other reasons or for detoxification.

- Neuropathy is more prevalent in frequent, heavy, and continuous drinkers compared to more episodic drinkers . When electrodiagnostic criteria are added, neuropathy detection increases to 25-90%

Mortality/Morbidity: Johnson and Robinson studied the mortality rate of alcoholics with autonomic dysfunction.

- Their findings suggested that evidence of vagal neuropathy in long-term alcoholics is associated with a significantly higher mortality rate than in the general population (a reported 88% survival rate at 7 years in alcoholics with autonomic dysfunction as compared to 94% in the general population).

- Deaths due to cardiovascular disease are a major factor.

- Many deaths were attributed to strokes, since heavy alcohol consumption is a significant risk factor for stroke.

Sex:

- A high incidence of alcoholic polyneuropathy has been observed in women.

History: Clinical manifestations of alcoholic neuropathy can be summarized as slowly progressive (over months) abnormalities in sensory, motor, autonomic, and gait function. Patients might ignore early symptoms, and seek help only when significant complications develop. Symptoms are often indistinguishable from other forms of sensory motor axonal neuropathy.

- Sensory symptoms include early numbness of the soles, followed by dysesthesias of feet and legs, especially at night. "Pins and needles" sensation, which is reported commonly, progresses to severe pain that is described as burning or

lancinating. Symptoms start typically distally, to progress slowly to involve proximally (dying-back neuropathy). When symptoms extend to involve above the ankle level, the fingertips often get similarly involved, giving rise to the well-known stocking and glove pattern of sensory involvement. Paresthesia might become unpleasant, even painful.[15]

- Motor manifestations include distal weakness and muscle wasting.
- When proprioception becomes involved, sensory ataxia will occur giving rise to gait difficulty, independent of alcoholic cerebellar degeneration.

- Autonomic disturbances are seen less commonly than other neuropathic conditions (eg, diabetes).

    - Dysphagia and dysphonia are prominent secondary to degeneration of the vagus nerve. Other parasympathetic abnormalities include depressed reflex heart rate responses, abnormal pupillary function, sexual impotence, and sleep apnea.

    - Sympathetic dysfunction is rare but if present can produce orthostatic hypotension and hypothermia.

- Frequent falls and accidents are common. These are secondary to gait unsteadiness and ataxia that are caused by cerebellar degeneration, sensory ataxia, or distal weakness.

Physical: Examination shows distal sensory loss in lower extremities. In severe cases, the hands may be involved. In addition to distal atrophy and weakness, deep tendon reflexes usually are decreased or absent. Stasis dermatitis, glossiness, and thinness of skin of the lower legs are common findings. Hyperesthesia and hyperalgesia may be seen along with hyperpathia. Excessive sweating of the soles and dorsal aspects of the feet and of the palms and fingers is a common manifestation of alcoholic neuropathy and is indicative of involvement of the peripheral (postganglionic) sympathetic nerve fibers. Occurrence of trophic ulcers is rare.

Causes:

- Variants
    - Rare cases of acute or subacute alcoholic peripheral neuropathy have been described. They mimic Guillain-Barré syndrome, although biopsy and electrodiagnostic studies had revealed an axonal neuropathy, with normal CSF parameters. A causal but an unproven association with ethanol is present.[16]
    - Pressure palsies: Alcoholics with generalized axonal peripheral neuropathy are prone for pressure palsies at multiple sites. Associated nutritional deficiency and weight loss might potentiate the same. Neurapraxia is more common than axonotmesis, and recovery is often the rule, although elderly patients do poorly.

Lab Studies:

- The diagnosis is based on accurate history of prolonged and excessive alcohol intake, clinical signs and symptoms, and electrophysiologic testing. Behse and Buchtal suggested that a minimum of 100 mL of ethyl alcohol (3 L of beer or 300 mL of spirits) per day for 3 years will precipitate the neuropathy[17].

Other Tests:

- Electrophysiologic findings primarily reveal evidence of primary axonal sensory motor polyneuropathy.
    - Sensory conduction studies may be abnormal even before the advent of clinical symptoms.
        - Sural nerve sensory action potentials (SNAP) are reduced slightly to moderately in conduction velocity and SNAP amplitudes also are reduced.
        - As the condition worsens, the sensory potentials may become unobtainable. The median, radial, and ulnar nerves show the same response as the disease progresses.
    - Motor conduction studies of the lower extremities (tibial and peroneal nerves) may reveal a slight reduction in conduction velocity (not to exceed 70-80% of the lower limit of normal), with diminution of the compound muscle action potential (CMAP) amplitude with a slight prolongation in

distal latency. The upper extremity nerves follow the same pattern as time progresses.[18]

  - The tibial H reflex latency is prolonged and becomes unobtainable if the condition continues to progress. The F waves are obtained more easily but reveal slight to moderate prolongation of latency.

- Needle electromyography (EMG) examination of the distal muscles of the lower extremities shows active denervation as well as chronic changes in the form of re-innervation patterns.
  - Spontaneous activity (positive sharp waves and fibrillation) is seen in the tibialis anterior and gastrocnemius.
  - The motor unit action potentials are reduced in recruitment pattern, with high-amplitude, long-duration, and polyphasic motor units.

- Avaria Mde et al (2004) have demonstrated that prenatal alcohol exposure is associated with abnormalities in nerve electrical properties and that the pattern is different from that seen in adults, showing conduction slowing and decrease in proximal and distal amplitude. Inference can be made by demonstrating other abnormalities of alcohol abuse, particularly abnormal liver function test results and red cell macrocytosis. Thiamine levels are not consistently reduced, but the thiamine-mediated enzyme transketolase estimation is often abnormal.[19]

- Cerebrospinal fluid (CSF) is typically normal or might show a mildly elevated total protein level.

- Patients have an increased risk of compression neuropathy, and electrodiagnostic findings can be complicated by superimposed mononeuropathies that are present. Recent methods of demonstrating small-diameter fiber neuropathy, such as quantitative sensory testing and intraepidermal nerve fiber density, have been applied but need to be applied in large scale.

- Sural nerve biopsy often shows evidence of generalized distal axonal loss affecting both large and small fibers but without distinctive pathologic features.

- Autonomic testing of parasympathetic and sympathetic reflexes is often abnormal (25% in one study), including analysis of heart rate variability, Valsalva maneuver, handgrip, tilt table, and standing maneuvers . The pattern of abnormalities often resembles the changes in diabetes and other causes of autonomic failure.[17]

Histologic Findings: Pathologic findings of the peripheral nerve in alcoholic neuropathy generally are agreed to consist of axonal degeneration with secondary segmental demyelination.

Medical Care: Treatment is directed toward stopping further damage to the peripheral nerves and returning to normal functioning. These can be achieved by alcohol abstinence, a nutritionally balanced diet supplemented by all B vitamins, and rehabilitation. However, in the setting of ongoing ethanol use, vitamin supplementation alone has not been convincingly shown to be sufficient for improvement in most patients.

Prognosis:

- The prognosis of alcoholic neuropathy generally is good, as reported by Hillbom and Wennberg in their series of 10 patients.
    - Provided that alcohol intake is discontinued and other causes of neuropathy (eg, malignancy, diabetes, nerve trauma) are carefully excluded, clinical and electrophysiologic examinations returned to normal or near normal. This is independent of age.
    - Prognosis is generally better in patients who are healthy and well nourished. Recovery is presumed to be due to regeneration and collateral sprouting of damaged axons.
- Studies have shown that patients with mild-to-moderate neuropathy can significantly improve, but the improvement is usually incomplete in those with severe findings.

Hepatic disease–related neuropathy

Hepatic disease–related neuropathies, as with primary biliary cirrhosis (PBC), can be associated with autonomic dysfunction in 48% of patients. The cause of autonomic dysfunction in hepatic disease remains unclear, but it may be associated with toxic metabolite accumulation or related immune-mediated mechanisms. It may be reversible following liver transplantation. Maheshwari et al (2004) hypothesized that patients with autonomic neuropathies are more likely to develop hepatic encephalopathy due to a decreased intestinal transit time.[20] Although this group's study did not show an independent effect of autonomic dysfunction on hepatic encephalopathy, their findings did demonstrate that patients with autonomic neuropathies were more likely to develop new-onset hepatic encephalopathy. In general, patients present with symptoms of both sympathetic and parasympathetic dysfunction, with or without symptoms of somatic nervous system dysfunction [21] Some symptoms, such as those of orthostatic intolerance, are common in autonomic neuropathies, whereas other symptoms, such as complete anhidrosis, are rare as a primary manifestation.

Orthostatic hypotension is often the first recognized symptom and typically is the most disabling [22]. However, other autonomic symptoms can occur before syncope, and these include impotence or ejaculatory dysfunction, decreased sweating, and urinary incontinence. Careful attention to use and dosage of prescription medication as well as over-the-counter nutritional and other health or dietary supplements is important. Lightheadedness and low blood pressure upon rising, which can lead to unconsciousness in severe cases.

Ocular - Blurring then graying of vision, blacking out, tunnel vision, sensitivity to light, difficulty with focusing, reduced lacrimation, loss of pupillary size over time (which is often correlated with loss of visual symptoms)

Cardiovascular - Orthostatic onset of palpitations, nausea, tremulousness, presyncope with light-headedness, visual blurring, tinnitus, and even chest pain and shortness of breath Orthostatic hypotension may follow and is often associated with postprandial state, alcohol, exercise, or temperature-induced exacerbation of hypotension. Supine hypertension and a loss of diurnal variation in blood pressure may occur later.[23]

Micturition and defecation may induce presyncope. With worsening symptoms, episodes of syncope with complete loss of consciousness after standing may occur. In the most severe of autonomic neuropathies, orthostatic tolerance loss with inability to stand because of immediate syncope may occur. Episodes of palpitations, angina, dyspnea, and syncope may relate to cardiac arrhythmias as well.

Gastrointestinal - Constipation, episodic diarrhea, early satiety, increased gastric motility, dysphagia, bowel atony, bowel incontinence, gastroparesis in diabetes mellitus (which may cause food stasis and subsequent vomiting, hyposalivation, and altered sense of taste[24]

Renal - Nocturia, bladder urgency, bladder frequency, enuresis, incomplete bladder voiding, urinary retention, and urinary incontinence Sexual - Impotence (mainly parasympathetic) and loss of ejaculation (mainly sympathetic), retrograde ejaculation, and possibly, female sexual dysfunction Sweating - Anhidrosis or hypohidrosis,

compensatory hyperhidrosis, gustatorysweating (Watkins, 1987) (Hyperpyrexia may occur in severe anhidrosis.)

Temperature regulation - Hypothermia (from loss of shivering and inability to vasoconstrict to prevent heat loss) and hyperpyrexia (may be of concern to patients with anhidrosis who are exposed to high temperatures) Feet - Burning feet most commonly observed in small-fiber sensory neuropathy (itching of feet may precede burning), pruritus, dysesthesia, allodynia, hyperalgesia, nocturnal exacerbation of symptoms, dry skin, loss of distal leg hair, brittle nails, pallor, and cold feet

Techniques of physical examination

Detailed neurologic examination should be performed to detect a somatic peripheral neuropathy. Motor examination should concentrate on the strength and muscle bulk of distal muscles, as well as on deep tendon reflexes. Sensory examination should include assessment of painful and temperature stimuli, as well as light touch, vibration, and proprioception to distal extremities. An important finding on sensory examination is a stocking pattern of sensory loss, which suggests concurrent somatic neuropathy. Coordination and gait are important to assess for an ataxic component to any suspected peripheral neuropathy. Specific abnormalities in autonomic functioning can be detected by using physical examination techniques, including the following: Measurement of lying, sitting, and orthostatic blood pressures to detect a postural especially if more than 20 mm Hg of systolic pressure, or drop of 10 mm Hg in the presence of presyncopal

symptoms. Pulse should be measured concurrently to examine for loss of compensatory tachycardia and the presence of excessive tachycardia response in the case of POTS.[25]

- Measurement of blood pressure during isometric exercise (sustained hand grip). The patient squeezes a handgrip dynamometer with one hand to maximum capability. Following this, grip is then reduced to 25-30% of maximum pressure for approximately 5 minutes. The normal response for diastolic blood pressure is an increase of >16 mm Hg in the opposite arm.. Measurement of postprandial blood pressures. An abnormal result would be to measure a drop in systolic blood pressure of >20 mm Hg approximately 15-20 minutes after a meal. Measurement of multiple daily blood pressures to examine for diurnal fluctuation. A difference of <15 mm Hg with either systolic or diastolic blood pressure between daytime (awake) values and nighttime (sleeping) values could indicate presence of autonomic dysfunction[26].
- Measurement of heart rate and blood pressure during a cold pressor test with hand immersed in ice cold water for at least 1 minute. The contralateral arm blood pressure is measured, with a drop of >10 mm Hg in diastolic blood pressure considered to be normal.

- Measurement of blood pressure and heart rate beat by beat during monitored respiratory activity as well as with Valsalva maneuver.

- Examination for skin shriveling in response to holding the hand in water for a prolonged time.
- Examination of the palms, soles, and axillae for sweat.
- Examination of pupillary responses to light and accommodation.
- Examination for presence of Horner syndrome with light palpation of both sides of the face to determine unilateral anhydrosis, assessment of pupillary size to determine miosis, and assessment for ptosis. .

- Of note, ptosis in Horner syndrome is due to a sympathetic defect to Mueller muscle, which is found in both superior and inferior eyelids; therefore, Horner syndrome can produce a ptosis of both upper and lower eyelids.
- Examination of the oral cavity for excessive dental caries in xerostomia. Examination of the conjunctiva and cornea for excessive scratches or signs of trauma due to xerophthalmia. Palpation of the lower abdomen for detection of a distended bladder.

3. Aim of the Study

The study was conducted with following specific objectives in mind.

1. To investigate autonomic Dysfunctions in patients with cirrhosis of varied etiology (in both alcoholics and non-alcoholics)

2. To analyze characteristics of patients who develop autonomic dysfunction

3. To determine the relationship between severity of liver damage and extent of autonomic function impairment.

4. Materials and Methods:

Study Design : Case control study

The study was conducted in Government General Hospital, Chennai, during the period of April 2006 to March 2007.and protocol of the study was submitted to the ethical committee of the hospital and the approval was obtained .

The study was carried out on 40 patients with Cirrhosis (20 alcoholics - 80g of alcohol per day for 10 year and 20 non-alcoholics) and 40 age and sex matched controls in the Department of Medical Gastroenterology, Madras Medical College, Chennai.

The diagnosis of Cirrhosis was made, on history, clinical examination, laboratory parameters, ultrasonographic findings, and the presence of oesophageal varices. The controls were healthy volunteers with no history of alcohol consumption and normal clinical and biochemical parameters. A detailed clinical history with special reference to symptoms of autonomic disturbance was taken from each subject and a thorough physical examination including neurological assessment was carried out.

A careful and complete history, as well as clinical examination as per proforma was performed. Following investigations were done for all patients. Complete blood counts, Bleeding time, Clotting time, Prothrombin time, Urinalysis, Stool examination for parasite and occult blood, Blood Sugar, Urea, Electrolytes, Creatinine, Serum Bilirubin SGOT, SGPT, Alkaline Phosphatase, Total protein, Albumin, Globulin, Ascitic fluid

protein, albumin, SAAG, amylase, cell count and cytology, viral markers like HBsAg, AntiHCV Ab, serum Cerulopalsmin in selected cases, Chest X ray, USG abdomen, Doppler study of portal venous system (in selected cases), and UGI endoscopy.

Amount of ethanol intake, frequency and type were noted and so also about other drug usage. All the patients and the controls were subjected to a battery of five standard autonomic function tests as detailed below.

Statistical analysis was carried out using SPSS windows 11.5 version.

INCLUSION CRITERIA

1. Symptoms and signs of parenchymal liver disease in the form of jaundice, swelling of legs and abdomen, unexplained asthenia, fever, anorexia, altered sleep pattern, bleeding tendency, spider nevi , palmar erythema, dupytren's contracture, gynacomastia and astrexis.
2. High SAAG ascites and or evidence of portal hypertension by clinical, endoscopic, Doppler ultra sound examination, and liver biopsies were performed whenever feasible.

EXCLUSION CRITERIA

1. Patients diagnosed as acute viral hepatitis
2. Liver secondaries with known or unknown primaries.
3. Obstructive jaundice as evidenced by ultrasound, or ERCP
4. Cases diagnosed to have Budd-Chiari syndrome, VOD, EHPVO or non cirrhotic portal hypertension.
5. Cases where EHPVO or NCPF could not ruled out with certain after exhaustive testing
6. Subjects who were known diabetes mellitus, ischemic heart disease and other medical conditions, and drugs that causes autonomic disturbance were excluded from the study.

Tests reflecting sympathetic damage

Blood pressure response to standing

This test measured the subject's blood pressure with a sphygmomanometer while he was lying quietly and one minute after he was made to stand up. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic blood pressure standing. The test was repeated three times and the mean was calculated.[27]

Blood pressure response to sustained hand grip

The blood pressure of the patient was taken three times before the manoeuvre. A modified sphygmomanometer was used for sustained handgrip manoeuvre. The patient was asked to grip the inflatable rubber bag and apply maximum voluntary pressure possible. A reading from the attached mercury manometer was taken during maximum voluntary contraction.

Thereafter, the patient was asked to maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic blood pressure during the handgrip exercise and the mean of the three diastolic blood pressure readings before the handgrip began.

Tests reflecting cardiac parasympathetic damage

Heart rate response to Valsalva manoeuvre. The subject was seated quietly and then asked to blow into a mouthpiece attached to a manometer, holding it at a pressure of 40 mm Hg for 15 seconds while a continuous electrocardiogram (ECG) was recorded. The manoeuvre was repeated three times with one minute interval in between and results were expressed as:

Valsalva ratio = longest R-R interval after the manoeuvre ÷ shortest R-R interval during the manoeuvre. The mean of the three Valsalva ratios was taken as the final value.

Heart rate (R-R interval) variation during deep breathing

The subject was asked to breathe deeply at six breaths/min (five seconds "in" and five seconds "out") for one minute. An ECG was recorded throughout the period of deep breathing and onset of each inspiration and expiration was marked on ECG paper. The maximum and minimum R-R intervals during each breathing cycle were measured with a ruler and converted to beats/min. The results of the test were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats/min.

Immediate heart rate response to standing

The test was performed with the subject lying quietly on a couch while the heart rate was recorded continuously on an electrocardiograph. The patient was then asked to stand unaided and the point at starting to stand was marked on ECG paper. The shortest R-R interval at or around the 15th beat and the longest R-R interval at around the 30th beat after starting to stand were measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratios. Interpretation of tests was based on the works of Ewing and Clarke .The patients were categorised as normal, if none of the tests was

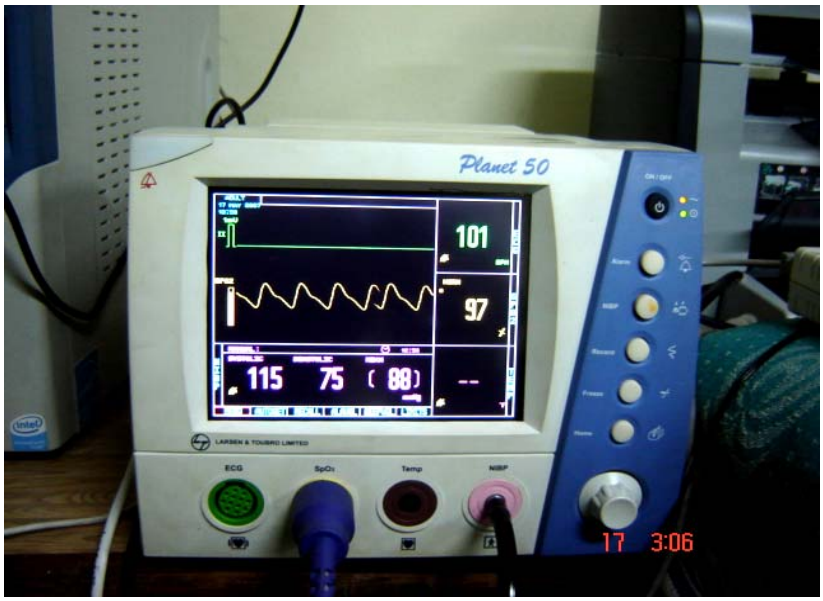
abnormal; with early parasympathetic damage, if results of one of the three tests of parasympathetic was abnormal; with definite parasympathetic damage, if two or more of the three tests of parasympathetic function were abnormal; and with combined damage, if one or both the tests of the sympathetic function were abnormal in addition to parasympathetic damage. For the purpose of the above mentioned classification the borderline tests were interpreted as normal.

A scoring system like the one suggested by Bellavere *et al* was also utilized to assess the extent of autonomic nervous damage[28] For each test "0" score was given for normal, "1" for borderline, and "2" for an abnormal value. By adding the score of each of the five standard tests of autonomic function, total autonomic function score was determined for every subject.

A comparison of frequency of symptoms of autonomic dysfunction was made between cirrhotics and controls, and between alcoholic and non-alcoholic groups. A simple set of clinical and laboratory features as devised by Child and Turcotte (later modified by Pugh and named Child-Pugh criteria) were used in the study to quantify the severity of liver damage in patients. Scoring is done on the basis of degree of ascites, encephalopathy, hypoalbuminaemia, hyperbilirubinaemia, and hypoprothrombinaemia.

The score of each of the parameters in an individual is added to classify a patient as belonging to Child class A, B, or C . This grading of cirrhosis was originally devised to help select patients with cirrhosis for portal systemic shunt surgery and it has been shown to have prognostic value in several studies.

Picture :1 . Instrument to assess heart rate and blood pressure response



Picture 2: Heart rate response to Deep breathing

Picture 3: Blood pressure response to sustained Hand Grip

Picture 4: Resting Heart rate variability.

5. Observations:

The study group includes 40 patients with Cirrhosis (20 alcoholics and 20 non-alcoholics) and 40 age and sex matched controls. Male:female ratio was 3:1. Twenty three (57.5%) were below 40 years of age. Common autonomic symptoms observed were dizziness while standing(75%), pain in extremities(7.5%), palpitation(12.5%), and constipation (5%). Nine (22.5%) had family history of jaundice. Of which 3 had HBsAg positive, 2 were diagnosed to have Wilson disease and remaining 4 did not have any identifiable etiologies.

Eleven (27%) patients had recent UGI bleed.Upper GI endoscopy showed Grade I (17), Grade II (15), Grade III (5) and 3 had no esophageal varices.

Eighty percent (32) of patients with Cirrhosis were found to have evidence of autonomic Dysfunction. Of these, six (15%) patients had early parasympathetic damage, ten (25%) had definite parasympathetic damage, and sixteen (40%) had combined (that is, both parasympathetic and sympathetic) damage.

Eighteen (90%) of the alcoholics and fourteen (70%) of the non-alcoholics had autonomic dysfunction.. Moreover, there was no significant association between subjective symptoms of autonomic dysfunction and objective evidence of autonomic damage as assessed by autonomic function tests. Autonomic dysfunction was significantly more frequent in advanced liver disease compared with early liver damage. One patient (50%)in Child A group , Eighteen (75%) out of 24 patients with Chronic

liver disease belonging to Child class B and 13 (92.85%) of the 14 patients belonging to Child class C had autonomic dysfunction..

The mean total autonomic function score were 0.45 for controls , 3.95 in Child class B and 6.53 in class C.(p value = 0.03) by (Mann-Whitney U test). The mean autonomic function scores for alcoholics and and non-alcoholics were 5.70 and 3.65 respectively.(p value = 0.72 by Mann-Whitney U test). In this study, heart rate response to standing was the most frequently (22 out of 40 patients) abnormal test in test group. In the present study, seven patients had abnormal heart rate response to deep breathing, twelve had abnormal blood pressure response to sustained handgrip, and eleven patients had an abnormal Valsalva ratio.

Table.1 : Child Turcotte Pugh score

Parameters	Child A	Child B	Child C
Ascites	none	slight	Moderate/severe
Encephalopathy	none	slight /moderate	Moderate/severe
Bilirubin mg/dl	<2.0	2-3	>3.0
Albumin g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time	1-3	4-6	>6.0

Table.2: Interpretation of autonomic function tests as normal, borderline, or abnormal depending on the value of the parameter measured

Test	Predominant Autonomicfunction tested	Normal	Border line	Abnormal
Valsalva ratio	parasympathatic	>1.21	1.11-1.20	<1.10
Deep breathing (Max-Min heart beat /min)	parasympathetic	>15	11-14	<10
Heart response to standing(30:15 ratio)	parasympathetic	>1.04	1.01-1.03	<1.00
BP response to standing (fall in blood pressure in mm Hg)	Sympathetic	<10	11-29	>30
BP response to sustained hand Grip (increasein diastolic pressure in mm of Hg)	Sympathetic	>16	11-15	<10

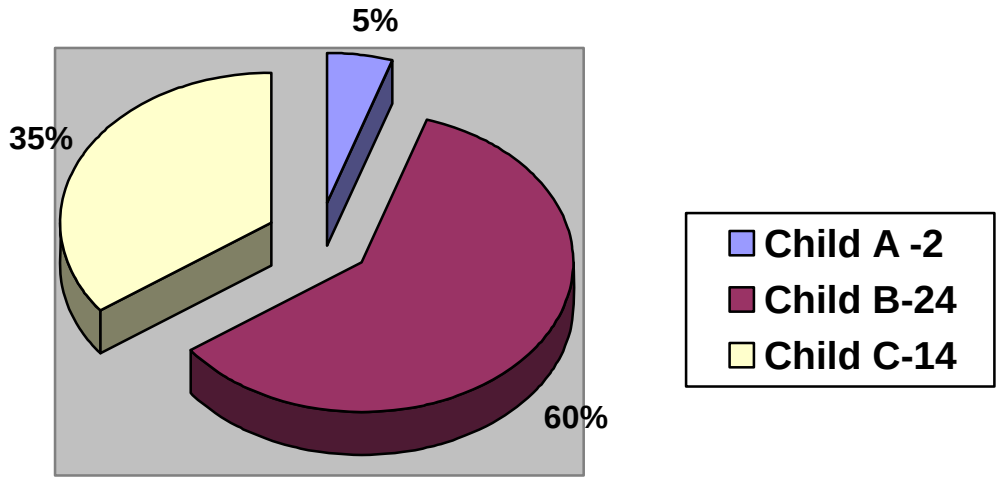
Table.3 Distribution of autonomic dysfunction according to Child class

Group	Child class A (n=2)	Child class B (n=24)	Child class C (n=14)
Early parasympathetic damage	1	4	1
Definite parasympathetic damage	0	6	4
Combined damage	0	8	8
Total	1	18	13

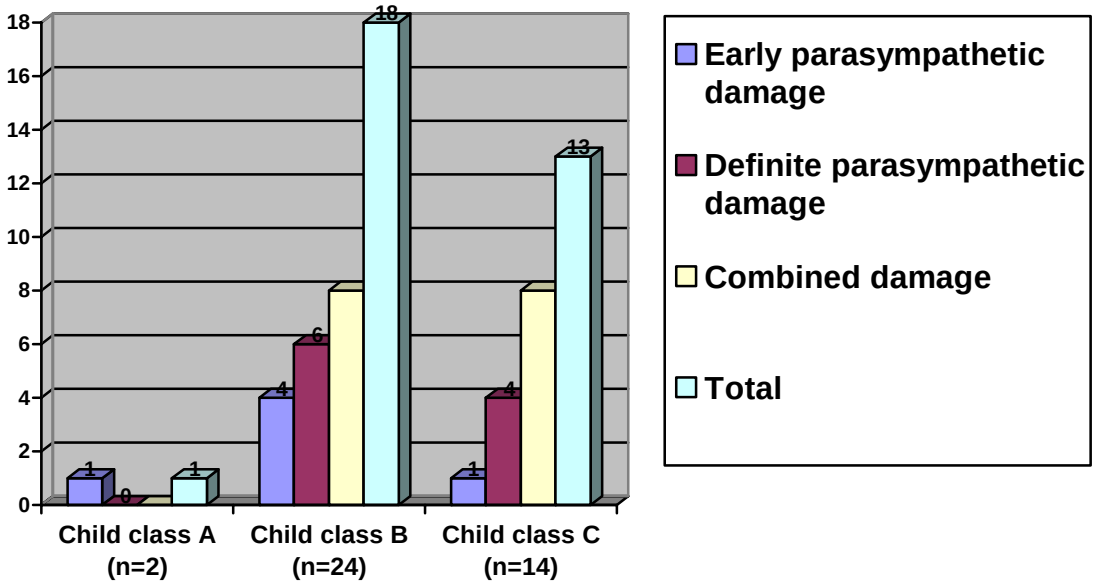
Table.4 Distribution of autonomic dysfunction in alcoholics and non alcoholics

	Parasympathetic damage			
Group	early	definite	sympathetic	combined
Total (n=40)	6	10	16	16
Alcoholics (n=20)	2	6	10	10
Non Alcoholics(n=20)	4	4	6	6

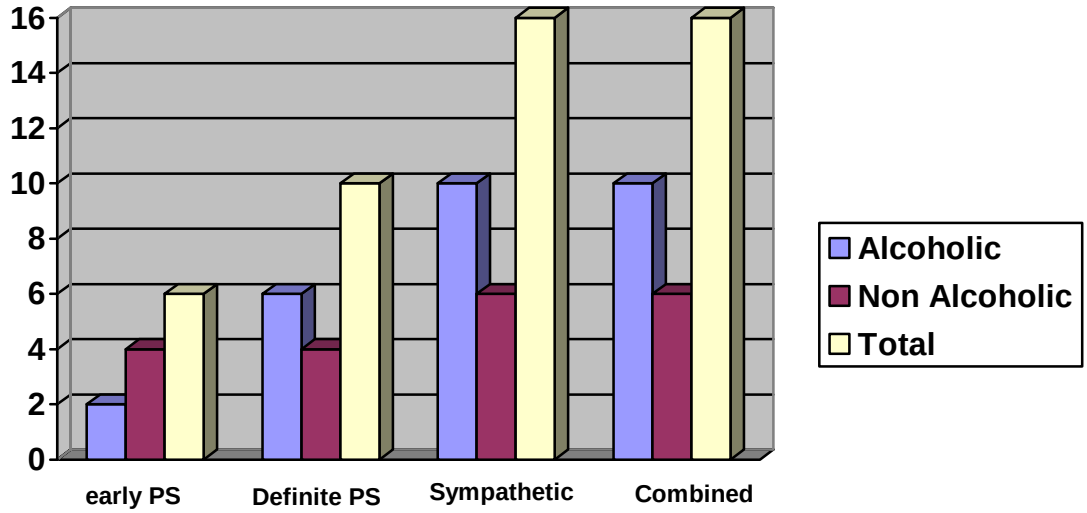
Graph:1 Distribution of Child Class in the study population



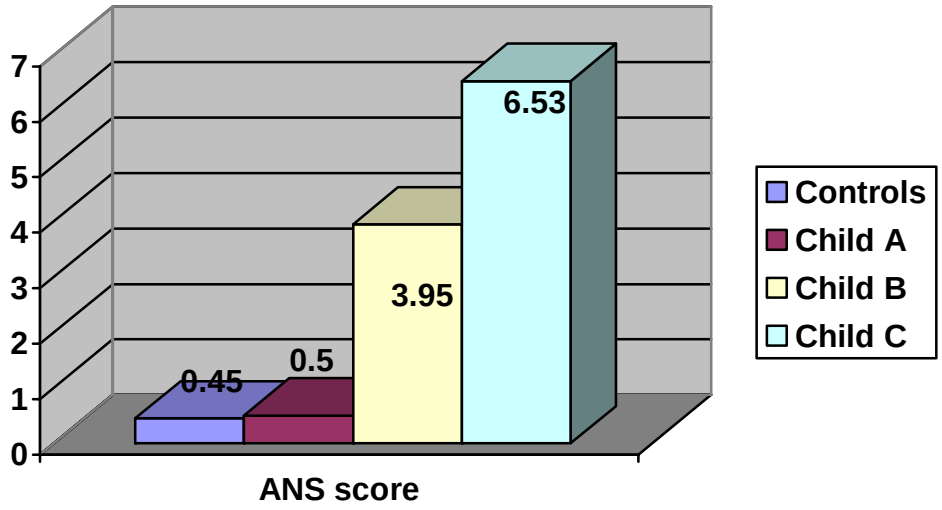
Graph:2 Distribution of autonomic dysfunction according to Child class



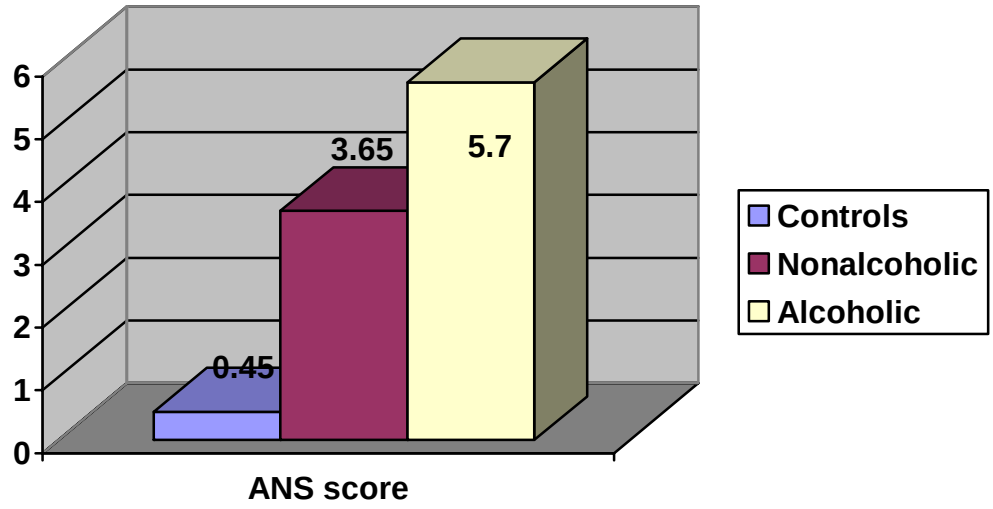
Graph:3 Distribution of autonomic dysfunction in alcoholics and non alcoholics



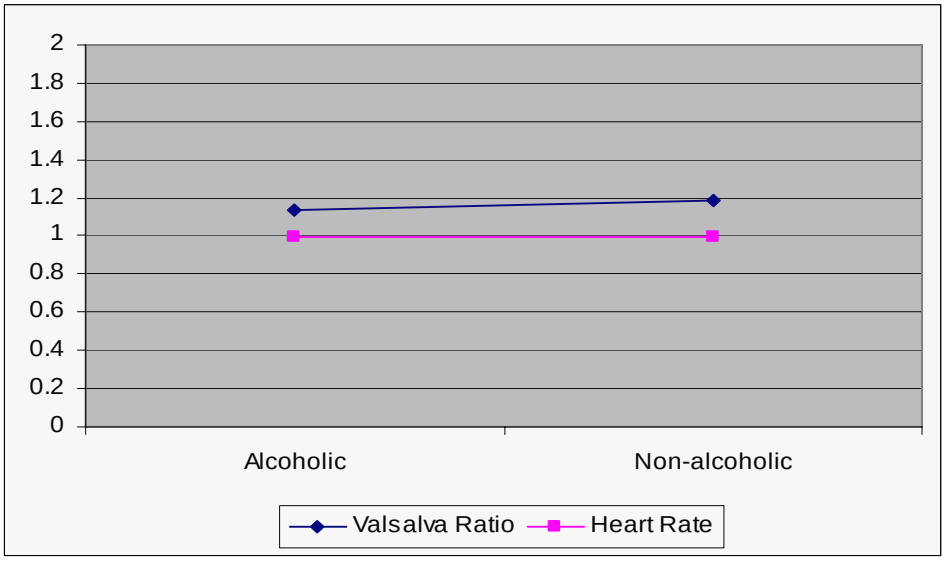
Graph:4. Distribution of autonomic score in patients according to their Child class



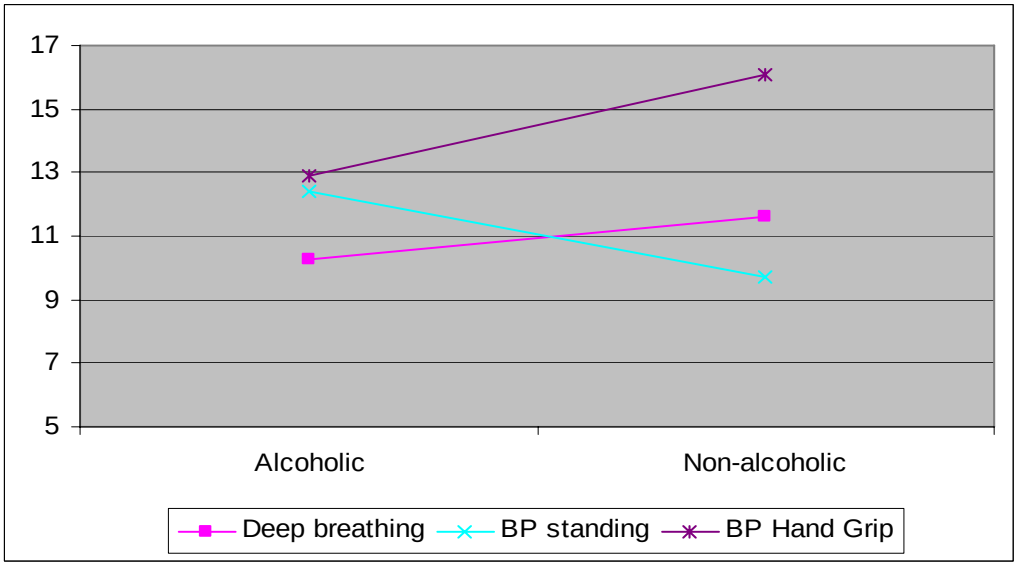
Graph:5. Distribution of autonomic score in alcoholics and non alcoholics



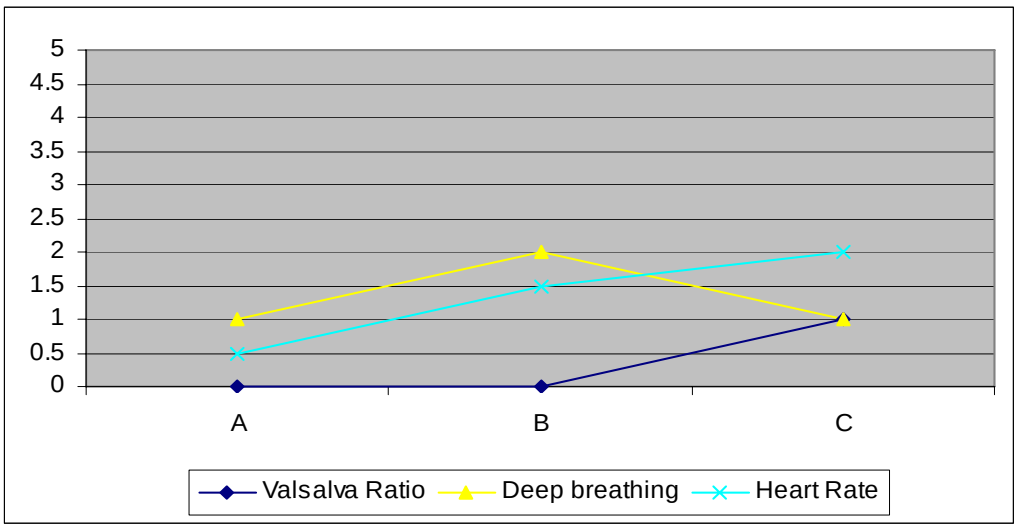
Graph 6. Comparison of Valsalva ratio and Heart rate response to Standing in alcoholic and non alcoholic Groups



Graph 7: Comparison of Heart rate response to deep breathing ,BP response to standing and BP response to sustained hand grip in alcoholic and non alcoholic Groups



Graph 8: Comparison of Valsalva ratio ,Heart rate response to deep breathing, Heart rate response to standing in Child A, B. and C groups



6. Discussion:

Autonomic nervous dysfunction is a known complication of diabetes[28] and alcohol abuse. Autonomic damage is expected in some patients with alcohol related cirrhosis since autonomic dysfunction, especially of vagal origin, is seen in chronic alcoholics[29]. Evidence for vagal neuropathy in alcoholic cirrhosis is well established by various studies[30] However, in non-alcoholic cirrhosis there are conflicting reports.[31]

Patients with cirrhosis and ascites have an activation of the sympathetic nervous system, as suggested by a higher than normal level of plasma norepinephrine, an augmented total body and individual organ norepinephrine spill-over rates, and an increased sympathetic nerve activity directly assessed by microneurographic techniques. The activation of the sympathetic nervous system is believed to playa major role in the pathogenesis of sodium retention and ascites has suggested by the inverse relationship between plasma norepinephrine and the urinary sodium excretion that is often observed in these patients.The possible role of the autonomic nervous system in the regulation of systemic hemodynamics in cirrhosis has been evaluated using cardiovascular tests such as the deep breathing, the 30:15 ratio, and the Valsalva ratio tests, which are considered to estimate parasympathetic activity. The results of these tests were frequently abnormal in patients with both alcoholic and nonalcoholic liver diseases. Indeed, 43% of patients with nonalcoholic liver diseases had an abnormal Valsalva ratio, RR variations in deep breathing, and response to intravenous atropine, suggesting a dysfunction of the parasympathetic nervous system.

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In our study, 32 of the 40 chronic liver disease patients (80%) were found to have an abnormal result in one or more autonomic function tests. However, Barter and Tanner in their study of 30 subjects reported evidence of parasympathetic damage in 16% and of combined parasympathetic and sympathetic neuropathy in an additional 20%..The lower frequency of autonomic dysfunction in their study could be due to the fact that they included only 14 subjects with alcoholic liver disease while the rest had an alcohol dependence problem only.

Szalay *et al* in their evaluation of 121 patients with chronic alcoholism—33 without liver disease, 33 with fatty liver, 33 with cirrhosis, 10 with biliary cirrhosis, and 12 with cirrhosis of another origin—found autonomic reflex damage in all.They observed significantly more damage in those with liver disease. Hendrickse and Triger reported cardiovascular autonomic dysfunction with predominantly parasympathetic abnormality in 35% of the patients with chronic liver disease.[33]

Hendrickse *et al* in another study reported vagal neuropathy in 45% of the 60 patients of chronic liver disease studied.. The lower frequency of neuropathy is probably due to inclusion of mostly Child class A patients in the study (57 of the 60 patients)[34.] Moreover, the study included a heterogeneous group of chronic liver disease patients with varying degrees of liver damage. In the present study, only one patient belonged to Child class A and the rest were class B or C.

Gentile *et al* found autonomic dysfunction in 60% (71% in the alcoholic group and 57% in the non-alcoholic group) of the 113 cirrhotics studied.[35]Like in the present study, alteration of parasympathetic function was significantly more frequent than that of sympathetic function. Dillon *et al* also detected abnormal cardiovascular reflexes in 60% of 70 cirrhotics.[36] Their study group included as many as 42 patients belonging to Child class A and only 15 patients in class C.

Gonzalez-Reimers *et al* have remarked in a study that in alcoholics, autonomic and peripheral neuropathy are dependent on each other and there is only weak correlation between liver function and both autonomic and peripheral neuropathy. In the present study no apparent relationship was noticed between autonomic and peripheral neuropathy, and autonomic damage was observed to be more common than peripheral neuropathy. The main object of the present study was to examine autonomic dysfunction and so, while careful systematic clinical examination was done in all the subjects, it is probable that more sensitive electrophysiological measurement would have yielded a much higher proportion of peripheral nerve abnormalities.

Maheshwari -Thuluvath *et al* in their study remarked that Autonomic dysfunction is common in patients with chronic liver disease. For hitherto unknown reasons, in longitudinal studies, the presence of Autonomic dysfunction has been found to be an independent predictor of mortality in patients with cirrhosis. They hypothesized

that patients with Autonomic dysfunction are more likely to develop hepatic encephalopathy (HE) due to prolonged intestinal transit time. In their study, they examined the incidence of new-onset HE in patients with and without AN. Seventy-two patients (Child A/B/C = 35/31/6) without evidence of HE at the time of autonomic function testing (AFT) were followed for 39.5 +/- 27.3 months. The end point of the study was the development of new onset HE.

Patients were followed until death or liver transplantation. Of the 72 patients, 42 (58%) patients did not develop HE (group A) while 30 (42%) developed HE (group B) during the follow-up. Both groups had similar baseline demographics. AN was more common in group B (27/30; 90%) compared to group A (28/42; 67%) (P = 0.02). Kaplan-Meier analysis showed a trend toward a higher incidence of HE in patients with Autonomic dysfunction . Mortality was higher in group B (12/30; 40%) compared to group A (8/42; 19%) (P = 0.04). Patients with Autonomic dysfunction were more likely to develop new onset HE. Although an independent effect of Autonomic dysfunction on HE was not established in that study, they speculated that delayed intestinal transit secondary to Autonomic dysfunction may explain the higher incidence of HE in patients with AN.

In the present study, eighteen (75%) out of 24 patients belonging to Child class B had autonomic dysfunction while 13 (92.85%) of the 14 patients in class C had impaired autonomic function. One patient (50%) in Child class A had autonomic damage. The mean total autonomic function score were 0.45 for controls were 0.45 for controls , 3.95 in Child class B and 6.53 in class C. .(p value = 0.03) The mean autonomic function

scores for alcoholics and and non-alcoholics were 5.70 and 3.65 respectively . These findings are similar to the observations of most other studies,[37,38] which reported increasing frequency of autonomic dysfunction with increasing severity of liver damage.

Hendrickse and Triger reported a strong correlation between the abnormal tests and Child-Pugh score ($p<0.0001$). In their study, they found autonomic dysfunction in 69% of Child class B and C patients and 23% in class A patients ($p<0.0001$). On the contrary, Gonzalez-Reimer *et al* in their study of 33 alcoholics, 20 of them cirrhotics, found a weak correlation between liver function and both autonomic and peripheral neuropathy.

Statistical comparison of cirrhotics and controls and alcoholics and non-alcoholics revealed that light headedness on standing was significantly more frequent in cirrhotics compared with controls ($p=0.001$). However, no statistically significant association was noted between other symptoms or signs of autonomic dysfunction. This is similar to the findings of most of the studies available which found poor correlation between symptoms of autonomic dysfunction and objective evidence of autonomic dysfunction as assessed by the autonomic function tests[39,40]. In our study, no statistically significant difference was observed for various clinical features and laboratory parameters of liver failure between those with and without autonomic dysfunction. This is in contrast to the findings of Hendrickse *et al* who observed that patients with vagal

neuropathy were significantly older and tended to have lower serum albumin than those with normal cardiovascular test.[41,42]

In our study, heart rate response to standing was the most frequently (22 out of 40 patients) abnormal test in test group. Barter and Tanner in their study noted the heart rate response to standing as the most sensitive test with high specificity. Thuluvath and Triger in their study reported the heart rate response to deep breathing as the most sensitive test. However, it is noteworthy that this test depends on the cooperation of the subject and is, thus not as reproducible as the heart rate response to standing..

Gentile *et al* remarked that deep breathing test and handgrip tests are the most influenced by the compliance of the patient. In the study, they found the deep breathing test and lying to standing (heart rate response) tests to be most altered and the most sensitive and specific tests respectively. . In the present study, seven patients had abnormal heart rate response to deep breathing, twelve had abnormal blood pressure response to sustained handgrip, and eleven patients had an abnormal Valsalva ratio.

Finally, considering the adverse prognostic implications of autonomic dysfunction reported in cirrhotics, further prospective studies involving a larger number of patients are warranted to delineate the factors responsible for the derangement and find remedial measures if possible.

7. Conclusion:

This study shows that autonomic dysfunction is common in patients with cirrhosis and it was comparable frequency both in alcoholics and non-alcoholics. It increases in severity with increase in extent of liver damage, suggesting that liver damage contributes to the neurological dysfunction

8. Summary:

It has been reported that the severity of autonomic dysfunction is proportional to the severity of cirrhosis, and its presence is an indicator of poor prognosis.
This study was conducted to investigate autonomic Dysfunctions in patients with cirrhosis of varied etiology, and to determine the relationship between severity of liver damage and extent of autonomic function impairment.

- The present study included 40 patients with Cirrhosis and 40 age and sex matched controls.
- All the patients and the controls were subjected to a battery of five standard autonomic function tests. (Valsalva ratio, HR response to deep breathing, Heart rate response to standing, BP response to standing & BP response to sustained hand Grip)

- Eighty percent (32) of patients with Cirrhosis were found to have evidence of autonomic Dysfunction. Of these, six (15%) patients had early parasympathetic

damage, ten (25%) had definite parasympathetic damage, and sixteen (40%) had combined (both parasympathetic and sympathetic) damage.

- Eighteen (90%) of the alcoholics and fourteen (70%) of the non-alcoholics had autonomic dysfunction.
- Autonomic dysfunction was significantly abnormal in advanced liver disease compared with early liver damage.
- Light headedness on standing was the most common symptom of autonomic dysfunction which was more frequently observed in cirrhotics compared with controls ($p=0.001$).
- One patient (50%) in Child class A group, eighteen (75%) in Child class B and 13 (92.85%) in Child class C had autonomic dysfunction.
- There was no significant association between symptoms of autonomic dysfunction and objective evidence of autonomic damage
- None of our patients was found to have sympathetic dysfunction alone.
- Parasympathetic damage was always found in association with an evidence of sympathetic damage.
- The mean (SD) total autonomic function scores in patients with cirrhosis and controls were 4.57(1.84) and 0.45 (0.57) respectively and it was statistically significant ($p<0.01$).
- Total autonomic function scores in alcoholics (5.70), and non-alcoholics (3.65) were not found to be statistically significant ($p>0.05$).

- Autonomic dysfunction was found to be proportional to the severity of cirrhosis. The mean total autonomic function score in Child class B and in class C were 3.95 & 6.53 respectively.

9. Annexure –I

Proforma

Date:

GE no:

1. Name :

2. Age/sex :

3. Address :

4. **History**

Abdominal distension

Abdominal pain

UGI bleeding

Jaundice

Altered sensorium

Fever

Pedal edema

Symptoms of autonomic dysfunction :

1. Dizziness while Standing
2. Altered sweating
3. Pain in extremities - exposure to cold Reynaud's phenomenon
4. Palpitation

5. Constipation
6. Nausea, vomiting
7. Difficulty in swallowing
8. Feeling full after eating little
9. Eye irritation/decreased lacrimation
10. Urinary frequency/ hesitancy

5. Drug history :

6. Family History :

7. Habits :

Alcohol abuse

8. BMI :

9. General examination :

10. Abdominal examination:

11. Investigations:

Liver function test :

CTP score :

USG abdomen :

UGI Endoscopy :

Autonomic function tests

12.Basal Recordings

- **Heart Rate**
- **Blood Pressure**

13.Orthostatic standing Test

- **HR (30/15)**
- **B.P. (supine)**
- **B.P. Standing**

14.Deep Breathing

- **HR**

15.Valsalva Maneuver

- **HR**

16.Isometric Hand Grip

- **B.P**

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Master Chart Control Group

S.No	Age	sex	AN symptoms	Drug history	Family History	Total	Valsalva ratio	Score	Deep breath	score	HR	Score	BP 1	score	BP 2	score	
1	40	2	0	2	0	1	1.22	0	16	0	1.05	0	16	1	16	0	
2	30	1	0	2	0	1	1.24	0	16	0	1.06	0	12	0	18	0	
3	35	1	0	2	0	1	1.24	0	18	0	1.08	0	14	1	20	0	
4	46	2	4	2	0	1	1.22	0	18	0	1.06	0	14	1	20	0	
5	32	1	0	2	1	1	1.28	0	16	0	1.07	0	12	0	18	0	
6	55	1	4	2	0	1	1.26	0	17	0	1.06	0	14	1	18	0	
7	46	1	1	2	0	0	1.23	0	17	0	1.06	0	6	0	20	0	
8	15	1	1	2	1	0	1.24	0	16	0	1.06	0	6	0	18	0	
9	27	2	4	2	0	0	1.22	0	18	0	1.08	0	8	0	18	1	
10	42	2	4	2	0	0	1.23	0	16	0	1.07	0	6	0	18	1	
11	37	1	1	2	1	0	1.24	0	17	0	1.09	0	6	0	16	0	
12	30	1	1	2	1	0	1.26	0	16	0	1.08	0	8	0	16	1	
13	40	1	1	2	1	0	1.22	0	18	0	1.06	0	6	0	16	0	
14	25	2	1	2	0	0	1.25	0	18	0	1.06	0	8	0	18	1	
15	37	1	0	2	1	0	1.22	0	18	0	1.08	0	6	1	18	0	
16	40	1	5	2	1	0	1.26	0	16	0	1.08	0	6	0	16	0	
17	36	1	0	2	1	0	1.26	0	16	0	1.06	0	4	0	20	1	
18	45	2	0	2	1	0	1.26	0	18	0	1.08	0	8	0	20	0	
19	34	1	0	2	1	0	1.22	0	16	0	1.06	0	6	0	18	0	
20	45	2	0	2	1	1	1.28	0	12	1	1.06	0	4	0	14	0	
21	40	1	1	2	0	1	1.26	0	14	1	1.06	0	6	0	12	1	
22	47	1	1	2	1	1	1.12	1	12	1	1.08	0	6	0	12	0	
23	34	1	1	2	1	1	1.18	1	12	1	1.08	0	6	0	16	1	
24	45	1	1	2	0	1	1.24	0	14	1	1.06	0	8	0	12	1	
25	41	1	1	2	1	0	1.22	0	16	0	1.06	0	8	1	12	0	
26	26	1	1	2	1	0	1.26	0	16	0	1.07	0	6	0	12	1	
27	35	2	3	2	0	1	1.24	0	14	1	1.08	0	8	0	12	0	
28	22	2	6	2	0	1	1.22	0	16	0	1.06	0	12	1	12	1	
29	33	1	0	2	0	1	1.24	0	18	0	1.06	0	14	1	14	0	

S.No	**Age**	**sex**	**AN symptoms**	**Drug history**	**Family History**	Total	Valsalva ratio	Score	Deep breath	score	HR	Score	BP 1	score	BP 2	score
30	35	1	0	2	0	1	1.24	0	18	0	1.06	0	12	1	12	1
31	42	1	0	2	0	0	1.26	0	16	0	1.06	0	8	0	18	0
32	41	2	0	2	1	0	1.24	0	16	0	1.07	0	6	0	18	0
33	18	1	0	2	1	0	1.22	0	16	0	1.09	0	6	0	20	0
34	24	2	0	2	0	0	1.22	0	18	0	1.06	0	6	0	20	0
35	34	1	5	2	0	1	1.24	0	16	0	1.04	1	8	0	18	0
36	46	1	6	2	1	1	1.14	1	16	0	1.06	0	6	0	20	0
37	40	2	0	2	1	0	1.22	0	18	0	1.08	0	8	0	18	0
38	38	1	0	2	1	0	1.23	0	16	0	1.02	1	6	0	20	0
39	20	2	0	2	1	0	1.22	0	16	0	1.06	0	8	0	18	0
40	27	2	0	2	0	0	1.24	0	18	0	1.06	0	6	0	16	0

Male -1
Female -2

1. Dizziness while Stanc 1.yes
2. Altered sweating 2.no
3. Pain in extremities
4. Palpitation
5. Constipation
6. Nausea, vomiting
7. Difficulty in swallowing
8. Feeling full after eating little
9. Eye irritation/decreased lacrimation
10. Urinary frequency/ hesitancy

1.jaundice
2.diabetes
3.HT

Valsalva ratio	Deep breathing test (max-min heart rate beats/min)	Heart rate response to standing (30:15 ratio)	BP 1 response to standing	BP 2 response to sustained hand grip
>1.21= 0	>15 = 0	>1.04 = 0	<10 = 0	>16 = 0
1.11–1.20 = 1	11–14 = 1	1.01–1.03 = 1	11–29 = 1	11–15 = 1
<1.10 = 2	<10 = 2	<1.00 = 2	>30 = 2	<10 = 2

Master Chart Control Group

S.No	Age	sex	AN symptoms	Drug history	Family History	Total	Valsalva ratio	Score	Deep breath	score	HR	Score	BP 1	score	BP 2	score	
1	40	2	0	2	0	1	1.22	0	16	0	1.05	0	16	1	16	0	
2	30	1	0	2	0	1	1.24	0	16	0	1.06	0	12	0	18	0	
3	35	1	0	2	0	1	1.24	0	18	0	1.08	0	14	1	20	0	
4	46	2	4	2	0	1	1.22	0	18	0	1.06	0	14	1	20	0	
5	32	1	0	2	1	1	1.28	0	16	0	1.07	0	12	0	18	0	
6	55	1	4	2	0	1	1.26	0	17	0	1.06	0	14	1	18	0	
7	46	1	1	2	0	0	1.23	0	17	0	1.06	0	6	0	20	0	
8	15	1	1	2	1	0	1.24	0	16	0	1.06	0	6	0	18	0	
9	27	2	4	2	0	0	1.22	0	18	0	1.08	0	8	0	18	1	
10	42	2	4	2	0	0	1.23	0	16	0	1.07	0	6	0	18	1	
11	37	1	1	2	1	0	1.24	0	17	0	1.09	0	6	0	16	0	
12	30	1	1	2	1	0	1.26	0	16	0	1.08	0	8	0	16	1	
13	40	1	1	2	1	0	1.22	0	18	0	1.06	0	6	0	16	0	
14	25	2	1	2	0	0	1.25	0	18	0	1.06	0	8	0	18	1	
15	37	1	0	2	1	0	1.22	0	18	0	1.08	0	6	1	18	0	
16	40	1	5	2	1	0	1.26	0	16	0	1.08	0	6	0	16	0	
17	36	1	0	2	1	0	1.26	0	16	0	1.06	0	4	0	20	1	
18	45	2	0	2	1	0	1.26	0	18	0	1.08	0	8	0	20	0	
19	34	1	0	2	1	0	1.22	0	16	0	1.06	0	6	0	18	0	
20	45	2	0	2	1	1	1.28	0	12	1	1.06	0	4	0	14	0	
21	40	1	1	2	0	1	1.26	0	14	1	1.06	0	6	0	12	1	
22	47	1	1	2	1	1	1.12	1	12	1	1.08	0	6	0	12	0	
23	34	1	1	2	1	1	1.18	1	12	1	1.08	0	6	0	16	1	
24	45	1	1	2	0	1	1.24	0	14	1	1.06	0	8	0	12	1	
25	41	1	1	2	1	0	1.22	0	16	0	1.06	0	8	1	12	0	
26	26	1	1	2	1	0	1.26	0	16	0	1.07	0	6	0	12	1	
27	35	2	3	2	0	1	1.24	0	14	1	1.08	0	8	0	12	0	
28	22	2	6	2	0	1	1.22	0	16	0	1.06	0	12	1	12	1	
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32	41	2	0	2	1	0	1.24	0	16	0	1.07	0	6	0	18	0
33	18	1	0	2	1	0	1.22	0	16	0	1.09	0	6	0	20	0
34	24	2	0	2	0	0	1.22	0	18	0	1.06	0	6	0	20	0
35	34	1	5	2	0	1	1.24	0	16	0	1.04	1	8	0	18	0
36	46	1	6	2	1	1	1.14	1	16	0	1.06	0	6	0	20	0
37	40	2	0	2	1	0	1.22	0	18	0	1.08	0	8	0	18	0
38	38	1	0	2	1	0	1.23	0	16	0	1.02	1	6	0	20	0
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<1.10 = 2	<10 = 2	<1.00 = 2	>30 = 2	<10 = 2